REMARKS

Claims 67-93 were filed in the present application. In the Office Action mailed 31 March 2008, Claims 67-78 were withdrawn from consideration as being directed to a non-elected invention. Applicants herein add new Claim 94. Support for Claim 94 can be found throughout the Specification, for example, in Example 5. No new matter has been added.

Claims 79-94 are pending following entry of Applicants amendments.

I. The Claims are Enabled and Supported by an Adequate Written Description

The Examiner rejected Claims 79-91 and 83 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

Applicants respectfully disagree. Applicants address each of the Examiner's rejections below.

The Examiner alleges "Claim 79 introduces new matter in claiming a dosage range of 5-20 mg/kg/day. There is no disclosure of such dosage range in specification." (Office Action page 15).

Applicants respectfully disagree.

Specifically, Applicants respectfully submit that the specification discloses "Dosages may range from 0.5 to 200 mg/kg/day, preferably from 3 to 25-50 mg/kg/day, given as single or divided doses, preferably given by continuous infusion or divided into two to four dosages per day." (Specification, page 10, lines 9-12). Moreover, the Specification provides support for a dose of 15 mg/kg/day.

> "As shown in table 6, a regimen of 5mg/kg lysostaphin three times daily was the most efficacious treatment. An impressive statistic is that this treatment completely sterilizied the heart valve vegetation in all but one of the rabbits. This was far superior to the standard regimen used as a positive control in this infection model: 30 mg/kg vancomycin twice daily. A regimen of 5 mg/kg lysostaphin once daily was less efficacious than the thrice daily regimen, but was almost as good as vancomycin in reducing bacterial counts in the vegetation; in fact, the effect was not statistically different from the vancomycin group." (Specification, page 20, lines 18-28, see also Table 6).

Thus, Applicants respectfully submit that Claim 79 is enabled and finds ample support in the Specification.

The Examiner alleges "Claims [sic] 82 introduces new matter in claiming dosage of 15 mg/kg/day. The only mention of dosage of 15 mg/kg in specification is for administration twice daily (paragraph [0072] of PreGrant publication) which amounts to 30 mg/kg/day." (Office Action page 15).

Applicants respectfully disagree.

Applicants respectfully submit that the passage cited above from the Specification (page 20, lines 18-28) provides ample support for Claim 82 and newly added Claim 94. That is, 5 mg/kg administered thrice daily is 15 mg/kg/day.

Claim 85 has been cancelled rendering the Examiner's rejection moot.

The Examiner rejected Claim 92 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sterilizing vegetation on heart valve, allegedly does not reasonably provide enablement for complete sterilization of infection in any other organs within the treated patient. (Office Action pages 15-16).

Applicants respectfully disagree. Nonetheless, in order to further Applicants business interests and the prosecution of the application, yet without acquiescing to the Examiner's allegations and while reserving the right to prosecute the original or similar claims in the future, Applicants herein amend Claim 92. Applicants respectfully submit that amended Claim 92 is enabled and supported by an adequate written description.

Applicants respectfully request that the Examiner withdraw each rejection made under 35 U.S.C. §112, first paragraph.

II. The Claims are Not Obvious

The Examiner rejected Claims 79-89, 92 and 93 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zygmunt, Goldberg and Stark, and further in view of Oldham.

Applicants respectfully disagree.

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a ***reason*** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd., 06-1329, slip op. (Fed. Cir. June 28, 2007)*, at 13-14 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR,* 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

Applicants respectfully submit that the cited references do not teach, suggest nor enable each element of the claimed invention, thereby precluding a finding of *prima facie* obviousness. Additionally, the cited references do not provide, individually or in combination, a reasonable expectation of success for carrying out the claimed invention, and actually teach away from the claimed invention.

A) Zygmunt and Goldberg

Zygmunt is a review article that discusses various properties of lysostaphin. Zygmunt reviews a number of articles, including Goldberg.

Applicants respectfully submit that the combination of Zygmunt and Goldberg do not teach or suggest all elements of the present invention, do not provide a reasonable expectation of success for carrying out the invention, and actually teach away from the claimed methods.

In particular, Applicants respectfully submit that neither reference teaches a method of treating a staphylococcal infection in a human subject, comprising:providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 5 to 20 mg/kg/day (e.g., as recited in Claim 79). Moreover, the cited references do not teach or suggest

administering a dose of 15 mg/kg/day (e.g., as recited in Claim 82). The cited references also fail to teach or suggest the use of recombinant lysostaphin.

Goldberg teaches that dogs administered dosages between 5-20 mg/kg/day do not achieve the same result as dogs administered higher doses (e.g., 50 mg/kg/day). Specifically, dogs administered lower dosages in the presently claimed range displayed an increase in lysostaphin resistant strains and also relapse.

> "The largest proportions of isolates found to be resistant were in three dogs receiving small repeated doses. The emergence of resistant isolates in these dogs may have resulted from repeated exposure to small amounts of enzyme. These three dogs relapsed, perhaps as a result of the large proportion of resistant staphylococci, or perhaps because the small doses of enzyme were insuggienct to control the infection." (Goldberg, page 52, left column, beginning at second full paragraph).

Thus, Applicants respectfully submit that Zygmunt and Goldberg not only fail to teach or suggest a method of treating an established organ infection in a human subject via administering to the subject lysostaphin in a dose of 5-20 mg/kg/day, the teachings of Zygmunt and Goldberg actually teach away from the claimed methods.

In particular, Goldberg specifically teaches that lower dosages (e.g., in the claimed range) lead to the formation of lysostaphin resistant strains. Specifically, dogs 7, and 10 exemplify why one of ordinary skill in the art would be lead away from the claimed invention. Table 4 shows that dogs 7, and 10 displayed 83 and 66 %, respectively, lysostaphin resistant strains in the blood, and dog 7 displayed 94 % lysostaphin resistant strains in tissue. Thus, Applicants respectfully submit that the cited references direct one of ordinary skill in the art away from the claimed invention. In particular, one of ordinary skill in the art would understand Goldberg, and Zygmunt summarizing the same, to teach the use of higher doses (e.g., 50 mg/kg/day or more) that provide results not achievable with lower dosages (e.g., absence of resistant strains). For these reasons, the skilled person would be inclined to select a dosage regimen for lysostaphin that is characterized by high dose (e.g., at least 50 mg/kg), and not a dose of the claimed invention.

B) Stark

Applicants respectfully submit that Stark does not teach or suggest all elements of the claimed invention. That is, Stark does not teach or suggest a method of treating a staphylococcal

infection in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 5 to 20 mg/kg/day (e.g., as recited in Claim 79). Moreover, Stark does not teach or suggest administering a dose of 15 mg/kg/day (e.g., as recited in Claim 82). Stark also fails to teach or suggest the use of recombinant lysostaphin. Similarly, Stark does not teach or suggest a method of treating an established staphylococcal infection in a human subject, comprising: providing a subject with endocarditis; and administering to the subject a recombinantly produced lysostaphin in a dose of 15 mg/kg/day (e.g., as recited in Claim 94).

Applicants respectfully point out that it was unknown whether or not the single patient in Stark had an established infection of an organ (e.g., the heart). Thus, Stark fails to provide a teaching, suggestion or guidance to one of ordinary skill in the art that the claimed methods would be useful. In sharp contrast, Stark actually teaches that an "episode of flushing, mild hypotension, and tachycardia followed the intravenous administration of lysostaphin. Diphenhydramine hydocholoride (Benadryl) and epinephrine were used in the appropriate manner for anaphylaxis, and the reaction was controlled in 60 minutes." (Stark, page 240). Moreover, Stark further teaches away from the claimed invention because, to the extent that the patient's heart failure was due to bacterial infection, administration of lysostaphin did not clear such infection as the subject died as a result of congestive heart failure three days post administration of lysostaphin.

Applicants respectfully submit that the Examiner has acknowledged that Goldberg, Zygmunt and Stark, individually or in combination, fail to teach or suggest the use of recombinant lysostaphin (See, Office Action mailed 20 September 2008, page 6).

C) Oldham

Applicants respectfully submit that Oldham fails to supplement the deficiencies of Zygmunt, Goldberg and/or Stark to teach or suggest the claimed invention. In sharp contrast, Oldham actually leads one of ordinary skill in the art away from the claimed invention.

Oldham teaches the treatment of bovine mastitis using recombinant lysostaphin. Oldham does not teach or suggest a method of treating a staphylococcal infection in a human subject, comprising: providing a subject comprising a staphylococcal infection, wherein the infection

comprises infection of an organ; and administering to the subject a recombinantly produced lysostaphin in a dose of 5 to 20 mg/kg/day (e.g., as recited in Claim 79). Moreover, Oldham does not teach or suggest administering a dose of 15 mg/kg/day (e.g., as recited in Claim 82). Similarly, Oldham does not teach or suggest a method of treating an established staphylococcal infection in a human subject, comprising: providing a subject with endocarditis; and administering to the subject a recombinantly produced lysostaphin in a dose of 15 mg/kg/day (e.g., as recited in Claim 94).

Applicants respectfully submit that the cited references, individually or in combination, do not render predictable the claimed methods of the present invention. In particular, work with lysostaphin in the cited references showed limited reduction in kidney bacterial load in mouse models (e.g., in Zygmunt) and in heart valves and other organs in a dog endocarditis model (e.g., Goldberg) at doses ranging from 50 to 250 mg/kg treatment. Despite these high dosages used, effectiveness of the magnitude required in the treatment of severe staphylococcal infections was not observed. That it, the cited references would not have led one of ordinary skill in the art to predict the rapid and total sterilization (e.g., of heart valve vegetations) in subjects treated with a lysostaphin regimen of the claimed methods. Moreover, one of ordinary skill in the art could not have predicted, prior to the disclosure of the present invention, the unexpected effectiveness of lysostaphin against S. aureus endocarditis (e.g., as claimed in Claim 79 and 94) as compared to conventional treatments available in the art at the time of the invention.

Accordingly, Applicants respectfully request that the rejection of the Claims under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Respectfully submitted,

Date: September 2, 2008

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